REMARKS/ARGUMENTS

This submission is responsive to the nonfinal office action, dated June 26, 2008, a response to which is due on Dec. 26, 2008, and is accompanied by a petition for a three month extension of time and the required fee of $555. Accordingly, this submission is timely filed.

Favorable consideration is requested in view of the foregoing Amendments and following Remarks.

I. STATUS OF THE CLAIMS

Claim 24 is amended to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for this amendment is found throughout the specification as filed, *inter alia*, at page 59 lines 7-9.

With entry of this amendment, claims 14 – 28 and 41 – 53 are pending. Claim 24 was amended.

Applicants reserve their right to file continuation applications directed to any subject matter to which they are entitled or to file divisional applications under 35 U.S.C. § 121 during the pendency of this application.

No new matter has been added by way of these amendments.

II. REQUEST FOR RECONSIDERATION OF RESTRICTION REQUIREMENT:

The Examiner withdrew claims 29–34 and 38–40 from further consideration pursuant to 37 C.F.R. § 1.142(b), as being drawn to a nonelected invention, alleging that there was no allowable generic or linking claim. With respect to Applicants' election with traverse of Group II in the reply filed on May 20, 2008, the Examiner stated that the traversal was not found persuasive because in Applicants' specification, Applicants refer to the different embodiments of their invention (citing paragraph ([188]). The Examiner further stated that one embodiment involves adding the protein complex to the extraction surface (the invention of Group II) whereas the other embodiment involves forming the protein complex on the extraction surface (the invention of Group III) (paragraph ([188]), and concluded that the groups are distinct and would require an undue examination and search burden. The Examiner stated that the requirement is still deemed proper and was therefore made FINAL.

The Examiner further stated that newly submitted claims 43–48 are directed to an

invention that is independent or distinct from the invention originally claimed for the following reasons: the previously searched invention did not comprise elution with a solid phase extraction tube enrichment factor greater than 1 or 2, and the previously claimed invention did not comprise an extraction channel that is a capillary. The Examiner stated that since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits, and therefore claims 43–48 are withdrawn from consideration as being directed to a non-elected invention (citing 37 C.F.R. § 1.142(b) and MPEP § 821.03).

In response, Applicants submit there would be no serious burden on the Examiner to search the claims together. MPEP § 806.05(i) states as follows: "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." Applicants respectfully submit that examination of the claims of Groups II and III can be made together without serious burden, as evidenced by the relatedness of the subject matter classified identically in class 422. In addition, in the interest of advancing prosecution and relieving the backlog of applications before the USPTO, Applicants submit that the claims should be rejoined and examined together. Applicants therefore respectfully request that the Examiner rejoin withdrawn claims 29–34 and 38–40 and examine these claims on the merits.

With respect to claims 43–48, Applicants submit that claims 43–48 depend from claims 14 and 19, directly or indirectly, ***which claims have already been searched***. There can be no additional burden on the Examiner when the search and examination of the base claims has already been performed. In addition, the Specification identifies a preferred embodiment of the extraction channel as a capillary, and hence the species of extraction channels that are capillaries was encompassed within the scope of the original claims. The Examiner's attention is directed to the first paragraph of the Summary, page 2, lines 19-20, as well as throughout the Specification as filed. Accordingly, Applicants respectfully submit that restriction of claims 43–48 is improper and request rejoinder and examination of claims 43–48.

Applicant expressly reserves his right under 35 U.S.C. § 121 to file divisional applications directed to the nonelected subject matter during the pendency of this application.

III. EXAMINER'S RESPONSE TO AMENDMENT

Applicants appreciate the withdrawal of the rejections under Laursen *et al.* (U.S. Patent No. 6,429,192) and Hagen *et al.* (U.S. Patent No. 4,810,381).

IV. CLAIM OBJECTIONS

Claims 19, 22, 43 and 44 were objected to under 37 C.F.R. § 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The Examiner stated that these claims replace the method step c) of claim 14 and thus should be rewritten in independent form.

In response, Applicants respectfully point out that the Examiner has failed to afford claim 14 its full scope in making these objections. Claim 14 recites:

> 14. A method for extracting a multi-protein complex comprising the steps of:
> a. introducing a sample solution comprising the multi-protein complex into an extraction channel, said multi-protein complex comprising at least a first protein and a second protein, said extraction channel having an inner surface comprising an extraction surface that binds said multi-protein complex, whereby said multi-protein complex is adsorbed to said extraction surface;
> b. optionally passing a wash solution through the channel; and
> c. passing a first desorption solution through the channel, thereby eluting said first protein.

Step c of claim 14 recites that the first protein of the complex is eluted, but is silent regarding the fate of the second protein. Claims 18, 19 and 22 further recite:

> 18. The method of claim 14, wherein said second protein remains adsorbed to said extraction surface.
>
> 19. The method of claim 14, wherein the entire multi-protein complex is eluted.
>
> 22. The method of claim 19, wherein the first desorption solution does dissociate the multi-protein complex.

In addition, claims 43 and 44 recite:

> 43. The method of claim 19 wherein the entire multi-protein complex is eluted with a solid phase extraction tube enrichment factor greater than 1.

44. The method of claim 43 wherein the entire multi-protein complex is eluted with a solid phase extraction tube enrichment factor greater than 2.

These claims clearly describe further limitations to the method recited in claim 14, i.e., where the second protein remains adsorbed to the extraction surface, where the second protein is eluted along with the first protein (i.e., as the multi-protein complex), and where the multi-protein complex is eluted but in dissociated form. Claims 43 and 44 refer to claim 19 and the situation where the entire multi-protein complex is eluted, and further recite limitations regarding the enrichment factors to be utilized.

Thus, claim 14 is a generic claim and recites the most general situation, and dependent claims 15–28, and 41–53 (including objected to claims 19, 22, 43 and 44) recite specific narrower limitations of claim 14, further limiting the scope of the claim, as required by 37 C.F.R. § 1.75(c). Accordingly, Applicants respectfully submit that the objections have been overcome and request that the rejections be withdrawn.

V. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 19, 22, 43, and 44 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that these claims contradict the subject matter of claim 14 by replacing the method step c) of claim 14, and required clarification.

As discussed above with respect to the claim objections, Applicants respectfully submit that the Examiner has misconstrued claim 14, particularly step c) as reciting a particular embodiment, which is contradicted by further limitations of claims 19, 22, 43 and 44. In fact, step c of claim 14 encompasses all possible outcomes for the second protein of the multi-protein complex; it is the further limitations of the dependent claims that properly recite and define the specific outcomes encompassed by step c of claim 14. Accordingly, there is no contradiction, and no indefiniteness, and the rejection is in error. Applicants respectfully submit that the rejection of claims 19, 22, 43 and 44 have been overcome, and request that the rejections be withdrawn.

VI. REJECTIONS UNDER 35 U.S.C. § 102

Claims 14 and 17–18 stand rejected under 35 U.S.C. § 102(e) as being anticipated by

Agnew *et al.* (U.S. Patent Application Publication No. 2004/0171034, hereinafter "Agnew"). The Examiner stated that Agnew teaches a method for extracting a multi-protein complex comprising the steps of introducing a sample solution comprising the multi-protein complex into an extraction channel which has an inner surface comprising an extraction surface that binds the multi-protein complex, passing a wash solution through the channel and passing a first desorption solution through the channel, thereby eluding the first protein (citing paragraph ([0014]).

In response, Applicants traverse these rejections. First of all, the cited portion of Agnew does not teach, suggest or disclose the use of an ***extraction channel***, and instead discusses the use of conventional supports for enriching phosphoproteins. Thus, Agnew does not teach each and every limitation of the rejected claims. For at least this reason, Agnew cannot anticipate claims 14 and 17–18.

In addition, Applicants respectfully submit the Examiner erred in construing complex mixtures to be the same as a multi-protein complex. ***A complex mixture is not a multi-protein complex***. The term "complex mixture" is a term of art meaning simply that a sample is a mixture of many components, and Agnew's use of this term does not teach, suggest or imply the formation of a complex between any members of that mixture. Applicants respectfully submit that the Examiner has misconstrued Agnew in interpreting this reference to teach anything whatsoever with respect to multi-protein complexes. In the cited portion of Agnew (Background, paragraph [0014]), Agnew refers to the selective enrichment of phosphopeptides from ***complex mixtures*** using immobilized metal affinity chromatography (where metal ions such as Fe^{3+} or Ba^{3+} are bound to a chelating support). Agnew teaches that enrichment of phosphopeptides from a ***complex mixture of peptides or proteins*** can be effected by binding the phosphopeptides to this support, and then releasing them using high pH or phosphate buffer. Thus, Agnew does not teach anything even remotely related to multi-protein complexes, but instead is concerned solely with the enrichment of components of a complex mixture, in particular the phosphoprotein components.

Accordingly, for at least these reasons, Applicants respectfully submit that the rejection of claims 14 and 17–18 under 35 U.S.C. § 102(e) as being anticipated by Agnew has been overcome, and respectfully request withdrawal of the rejection.

Claims 14, 17–20, 22–24, 26–28, 41–42 and 49–53 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zimmerman *et al.* (U.S. Patent Re. 32,011, hereinafter "Zimmerman"). The Examiner alleged that Zimmerman teaches a method for extracting a multi-protein complex comprising the steps of introducing a sample solution comprising the multi-protein complex into an extraction channel which has an inner surface comprising an extraction surface that binds the multi-protein complex, passing a wash solution through the channel and passing a first desorption solution through the channel, thereby eluting the first protein (citing column 2, line 55–column 3 line 13). The Examiner further stated that the second protein remains adsorbed (column 3, lines 3 lines 3–4), the multi-protein complex comprises a protein antigen (abstract), a second desorption solution is passed through the extraction channel, thereby eluting the second protein (column 8, lines 49–53), the first and second desorption solutions differ in ionic composition (column 2, line 55–column 3, line 13; column 8 lines 49–53), and that the first desorption solution inherently contains an agent that effects protein-protein interactions. The Examiner also stated that desorption solutions are inherently flowed back and forth through the column due to fluid dynamics, the extraction surface is 3-dimensional and is comprised of an affinity binding agent consisting of a protein (column 6, lines 9–36), and the method is performed in a plurality of channels operated in parallel or in a solid block having one or more passageways running through (columns 7–8).

In response, Applicants respectfully traverse these rejections. Claim 14 recites:

> 14. A method for extracting a multi-protein complex comprising the steps of:
> a. introducing a sample solution comprising the multi-protein complex ***into an extraction channel***, said multi-protein complex comprising at least a first protein and a second protein, said ***extraction channel having an inner surface comprising an extraction surface*** that binds said multi-protein complex, whereby said multi-protein complex is adsorbed to said extraction surface;
> b. optionally passing a wash solution through the channel; and
> c. passing a first desorption solution through the channel, thereby eluting said first protein.

At a minimum, to anticipate claim 14 (and claims 17–20, 22–24, 26–28, 41–42 and 49–53 dependent thereon) Zimmerman would have to teach the ***use of an extraction channel***, in particular, one ***having an inner surface comprising an extraction surface***. As explained in the response dated August 1, 2007, the extraction channels of the instant claims are ***open*** channels that can be comprised of ***tubing*** such as fused silica capillary tubing. In Applicant's

specification, the extraction channels are defined as follows:

> The term "channel" encompasses but is not limited to the various forms of conventional capillary ***tubing*** that are used for applications such as chromatography and capillary electrophoresis, e.g., fused silica capillary tubing. Thus, the term also encompasses other ***open*** channels of similar dimensions, having one or more capillary flow passageways, each having an inlet and outlet. Examples include a capillary tube, a bundle of tubes, a solid block or chip having one or more passageways or flow cells running therethrough, e.g., a microfluidics device such as those associated with BiaCore, Inc. (Piscataway, NJ), Gyros, Inc. (Uppsala, Sweden), Caliper Technologies, Inc. (Mountain View, CA) and the like. (Specification, page 24, lines 5 – 13). [Emphasis added]

However, Zimmerman fails to teach this feature of the rejected claims.

The instant invention is further distinguishable from Zimmerman by the position of the extraction surface ***on the inner surface*** of the open channel. The position of the extraction surface is described in Applicant's specification as follows:

> In preferred embodiments, the extraction surface covers the entire ***inner periphery*** of the extraction channel, as opposed to on just one face of the channel. (Specification, page 8, lines 14 – 15).
>
> Fig. 1 shows a tubular channel 2, the ***inner surface of which is coated with a solid phase extraction medium*** 4. (Specification, page 19, lines 26 – 27). [Emphasis added]

In contrast, Zimmerman teaches a method of separating component molecules of the factor VIII/von Willebrand factor complex, VIII:C and CIII:RP, and purification and concentration of the pro-coagulant activity protein VIII:C. The method is described (at col. 2, line 55 – col. 3, line 13) as involving first immunoadsorbing factor VIII using an adsorbent comprising a monoclonal antibody specific for VIII:RP bound to a suitable substrate (such as agarose beads) and washing to remove and recover VIII:C, followed by concentrating the recovered purified VIII:C using affinity chromatography. In other words, Zimmerman teaches the use of a conventional packed bed medium such as agarose beads in its methods. Zimmerman further describes preparation of the immunoadsorbent at col. 6, line 8 – col. 7, line 32, and suggests the use of glass beads, agarose and derivatives thereof. At no point in Zimmerman is the use of an ***extraction channel*** contemplated, taught or suggested. Further, the extraction surface provided by beads suggested by Zimmerman provides an extraction surface primarily on the ***exterior*** of the beads, not an ***extraction channel having an inner surface comprising an***

extraction surface as required by claim 14. Accordingly, the Examiner's assertion that Zimmerman teaches the "introducing a sample solution comprising the multi-protein complex into an extraction channel which has an inner surface comprising an extraction surface that binds the multi-protein complex" is simply erroneous and cannot serve as the basis for the anticipation rejections made in the instant Office Action.

With respect to dependent claims 17–20, 22–24, 26–28, 41–42 and 49–53, the Examiner's assertions are similarly erroneous and irrelevant to the patentability of the instant claims. In particular, it is simply irrelevant whether the second protein remains adsorbed; whether the multi-protein complex comprises a protein antigen; whether a second desorption solution is passed through the extraction channel thereby eluting the second protein; or whether the first and second desorption solutions differ in ionic composition, since Zimmerman fails to disclose the use of an extraction channel, as required by claim 14. It is also irrelevant whether the first desorption solution inherently contains an agent that effects protein-protein interactions, again since Zimmerman fails to disclose the use of an extraction channel.

Similarly, it is irrelevant whether desorption solutions are inherently flowed back and forth through the column due to fluid dynamics. However, Applicants point out that this assertion is also in error: conventional chromatography techniques utilize unidirectional flow in order to minimize band broadening and additional dilution of product, hence bidirectional flow is specifically avoided in the practices described in Zimmerman. In addition, it is irrelevant whether the extraction surface is 3-dimensional and is comprised of an affinity binding agent consisting of a protein (column 6, lines 9–36), or the method is performed in a plurality of channels operated in parallel or in a solid block having one or more passageways running through (columns 7–8), because Zimmerman fails to disclose the use of an extraction channel, as required by the claims. In addition, the meaning of the term "3-dimensional" in the instant claims is different from the alleged use of a 3-dimensional extraction surface in Zimmerman: Applicants utilize an extraction channel which is ***open*** with an ***inner extraction surface***, not a packed bed of conventional chromatography medium as taught by Zimmerman. To the extent that the channel can be 3-dimensional, the instant specification (via U.S. Provisional Application No. 60/523,518 incorporated by reference therein) discloses, e.g., dextran derivatized capillaries. The use of polymer derivatized capillaries is very different from a column having a packed bed. Hence, the Examiner's rejection on this basis is also flawed.

Accordingly, Applicants respectfully submit that the rejection of independent claim 14, and claims 17–20, 22–24, 26–28, 41–42 and 49–53 dependent therefrom under 35 U.S.C. § 102(b) by Zimmerman has been overcome, and request withdrawal of the rejections.

VII. REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 15–16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman or Agnew, *supra*, in view of Gobom *et al.* ("Sample Purification and Prepartion technique Based on nano-scale Reversed-phase Columns for the Sensitive Analysis of Complex Peptide Mixtures by Matrix-assisted laser Desorption/ionization Mass Spectrometry", *J. Mass Spectrom.*, vol. 34 pages 105–116 (1999), hereinafter "Gobom"). The Examiner conceded that neither Zimmerman nor Agnew expressly teach purging the extraction channel with a gas prior to passing a desorption solution through the channel wherein the extraction surface remains substantially solvated after the purging step. However, the Examiner alleged that Gobom teaches a method of extracting proteins wherein the extraction channel is purged with a gas before adding the desorption solution (page 107, right column), and that Gobom teaches that this step is imperative for smooth and continuous liquid flow in the next step (page 107, right column). The Examiner alleged that it would have been obvious to modify Zimmerman or Agnew by purging the channel with gas before adding the desorption solution in order to gain the predictable results of a smooth and continuous liquid flow during the purification of the protein.

In response, Applicants respectfully traverse. Claims 15 and 16 recite:

> 15. The method of claim 14, wherein prior to step (c), the channel is purged with a gas so that said ***extraction channel*** is substantially ***free of bulk liquid***.
>
> 16. The method of claim 15, wherein said extraction surface ***remains substantially solvated after the purging step***. [Emphasis added]

In contrast, as discussed above, neither Zimmerman nor Agnew discloses the use of ***extraction channels***, as required in the instant claims. The addition of Gobom does nothing to relieve this deficiency: Gobom teaches the use of conventional reversed phase packed medium in the preparation of peptides for analysis using MALDI/TOF-MS. These particulate adsorbents, typically silica based, are also distinguishable from the open extraction channel of the instant claims. Hence, Gobom also does not disclose an ***extraction channel***, nor does it disclose a channel ***having an inner surface comprising an extraction surface***. Accordingly, the

combination of references cannot teach each and every limitation of the rejected claims, and thus cannot render the claims obvious. For at least this reason, the rejection of the claims as obvious is in error and should be withdrawn.

Further, the peptides analyzed in Gobom are low molecular weight compounds amenable to manipulation with nonaqueous solvents. The secondary (as well as tertiary and quaternary) structure of these peptides is of no relevance for MALDI/TOF-MS, and would be abolished by proteolytic treatment as well as by the harsh solvent conditions employed in Gobom. For example, in the cited portion of Gobom, a washing step of acetonitrile/0.1%(v/v) trifluoroacetic acid was utilized prior to elution of the peptides. These solvent conditions are not compatible with the desired objectives of the present application to preserve the native protein structures and extract multi-protein complexes.

In contrast, the methods of the instant claims require the use of aqueous solutions and gentle treatment of the multi-protein complex and its constituent molecules in order to prevent denaturation and irreversible damage. It is known in the art of protein purification that exposure of delicate proteins and multi-protein complexes to nonaqueous solvents and to air and air/solution interfaces can result in denaturation of the proteins. For example, the Specification states:

> Extractions of the invention typically involve the loading of analyte in a sample solution, an optional wash with a rinse solution, and elution of the analyte into a desorption solution. The nature of these solutions will now be described in greater detail. With regard to the sample solution, it typically consists of the analyte dissolved in a solvent in which the analyte is soluble, and in which the analyte will bind to the extraction surface. Preferably, the binding is strong, resulting in the binding of a substantial portion of the analyte, and optimally substantially all of the analyte will be bound under the loading protocol used in the procedure. ***The solvent should also be gentle, so that the native structure and function of the analyte is retained upon desorption from the extraction surface. Typically, in the case where the analyte is a biomolecule, the solvent is an aqueous solution***, typically containing a buffer, salt, and/or surfactants to solubilize and stabilize the biomolecule. Examples of sample solutions include cells lysates, hybridoma growth medium, cell-free translation or transcription reaction mixtures, extracts from tissues, organs, or biological samples, and extracts derived from biological fluids. (Specification, page 20, line 21– page 21, line 4)

One skilled in the art would not view the disclosure of Gobom as applicable to uses for native proteins or as useful for extracting a multi-protein complex. Further, the methods and solvent treatments taught by Gobom ***teaches away*** from the use of open extraction channels and

aqueous solutions as utilized in the instant application and claims. In fact, due to the distinguishable objectives and applications, Applicants submit that ***Gobom is not properly combinable*** with either Agnew or Zimmerman. In any event, Applicants respectfully submit that there would be no predictability in combining the teaching of Gobom regarding nonaqueous solutions, reversed phase adsorbents and peptides with the teachings of Agnew and Zimmerman regarding purification of intact proteins in their native state.

In addition, the Examiner cited Gobom as stating that the drying "is imperative for smooth and continuous liquid flow." However, this statement must be taken in context of the disclosure and objectives of Gobom: to elute peptides from a reversed phase medium for MALDI/TOF-MS. The use of a particulate adsorbent and low viscosity solvents is distinguishable from the methods of the instant claims. Drying the column as described by Gobom could evaporate volatile solvent, resulting in an unsolvated adsorbent, which is an outcome contraindicated by the present Specification and claims. There is also no predictability that drying the instant extraction channel comprising an extraction surface and utilizing higher viscosity aqueous solutions could be applied using the method of Gobom with good effect, i.e., without irreversible damage to the adsorbed analyte.

Further, the Examiner stated that "it would have been obvious to modify Zimmerman or Agnew by purging the channel with gas before adding the desorption solution in order to gain the predictable results of a smooth and continuous liquid flow during the purification of the protein." However, ***there is no teaching or requirement in the instant Specification and claims for "smooth and continuous liquid flow."*** The instant Specification states:

> Prior to elution of the adsorbed analyte from an extraction capillary, it is often desirable to purge any residual solution from the capillary, i.e., to blow out the capillary. This residual solution will typically be the wash solution if such is used, or the sample solution if there is not wash step. In some embodiments a purge step can be performed both before the wash step (e.g., to remove residual sample solution) and after the wash step, but purging is normally not necessary prior to the wash step. In certain embodiments, multiple wash steps are employed. For example, in some embodiments an extra D_2O wash is employed prior to elution in a deuterated solvent. Purging can be effected after such extra steps if desired. (Specification, page 13, line 30 – page 14, line 7)

The Specification also teaches: "Small particulates and air bubbles typically have little or no effect on performance, a remarkable distinction from previous solid phase extraction systems,"

(Specification, page 19, lines 9-11) and "In particular embodiments, the ***liquid flow is not continuous*** and smooth, for example, where a slug of liquid bounded by gas is used." (Specification, page 15, line 29 – page 16, line 4). Accordingly, for this additional reason – because it teaches that continuous liquid flow is required, Gobom ***teaches away*** from the instant claims. Further, ***the motivation to combine references is not found in the references themselves or in the art, but has been fabricated by the Examiner solely to provide the basis for this obviousness rejection***.

Accordingly, Applicants respectfully submit that the rejection of claims 15–16 under 35 U.S.C. § 103(a) over Zimmerman or Agnew in view of Gobom has been overcome, and request withdrawal of the rejection.

Claim 21 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman, *supra*. The Examiner conceded that Zimmerman does not expressly teach using a third desorption solution to elute a third protein. However, the Examiner alleged that Zimmerman provides all the necessary teaching for eluting more than one protein in a protein complex (column 2 line 55–column 3 line 13; column 8 lines 49–53), and that it would have been obvious for one of ordinary skill in the art to modify Zimmerman by using a third desorption solution to elute a third protein in order to obtain the predictable results of separating the third protein from the multi-protein complex.

In response, Applicants respectfully traverse. As discussed above, Zimmerman teaches the use of a conventional packed bed medium as an immunoadsorbent at col. 6, line 8–col. 7, line 32, and suggests the use of glass beads, agarose and derivatives thereof. At no point in Zimmerman is the use of an ***extraction channel*** contemplated, taught or suggested. It is irrelevant whether or not Zimmerman provides the "necessary teaching for eluting more than one protein in a protein complex" as alleged by the Examiner, since Zimmerman does not teach the use of an extraction channel, which is required in the pending claims. Accordingly, the Examiner's assertion that "it would have been obvious … to modify Zimmerman by using a third desorption solution to elute a third protein in order to obtain the predictable results of separating the third protein from the multi-protein complex" is simply erroneous and cannot serve as the basis for the obviousness rejections made in the instant Office Action.

Applicants respectfully submit that the rejection of claim 21 under 35 U.S.C. § 103(a)

over Zimmerman has been overcome, and request withdrawal of the rejection.

Claim 25 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman, *supra*, in view of Agnew, *supra*. The Examiner conceded that Zimmerman does not expressly teach an agent selected from urea, guanidinium chloride and isothiocyanate. However, the Examiner alleged that Agnew teaches purifying a protein by using an agent comprising reactive groups that bind to phosphate by interfering with protein-protein interactions (citing paragraphs [0104–0106]). The Examiner stated that these reactive groups include isothiocyanates and ureas (citing paragraph [0106]). The Examiner further stated that the advantage of these reactive groups is that they are photoactivatable (citing paragraph [0154]), and the advantage of photoactivatable reactive groups is that the resulting phosphate-binding compound that is useful for conjugation to phosphorylated target molecules (citing paragraph [0153]). The Examiner concluded that it would have been obvious to modify Zimmerman with the reactive groups of Agnew in order to gain the advantages of having a resulting phosphate-binding compound that is useful for conjugation to phosphorylated target molecules.

In response, Applicants respectfully traverse. In addition to the ***failure of either cited reference to teach the use of an extraction channel***, and hence the failure of the combined references to teach every element of the claimed invention, Applicants make the following additional points. Claims 24 and 25 recite as follows:

> 24. The method of claim 20, wherein at least one of the desorption solutions contains an agent that affects protein-protein interactions.
>
> 25. The method of claim 24, wherein the agent is selected from urea, guanidinium chloride and isothiocyanate.

Thus, claim 25 requires the use of an agent that affects protein-protein interactions, specifically urea, guanidinium chloride or isothiocyanate. While the Examiner is correct that Agnew discloses two of these agents as generic classes of compounds (isothiocyanates and ureas) in paragraph [0106]), it does so only as "reactive groups" "capable of reacting with another chemical group to form a covalent bond." (See [0105]) However, in the instant specification and claims, urea, guanidinium chloride and isothiocyanate are merely solution components that affect the structure and stability of proteins, not "reactive groups" as taught by Agnew. One skilled in the art would understand that the agents urea, guanidinium chloride and

isothiocyanate recited in claim 25 are widely used as protein denaturants, not as reactive groups, since these agents do not react with the proteins at all. Thus, the listing of exemplary reactive groups by Agnew is irrelevant to the use of the recited agents.

Applicants strongly submit that ***Agnew is not relevant to the patentability of the pending claims at all***. If anything, Agnew ***teaches away*** from the use of these compounds as an "agent that affects protein-protein interactions" as Agnew teaches that classes of compounds labeled ureas and isothicyanates are "reactive groups" that form covalent bonds. However, covalent bonding of reactive groups with the protein is a result that would be ***highly disadvantageous*** to one seeking to purify native proteins, in particular multi-protein complexes, since such chemical modification would alter the structure and function of the protein.

Further, the Examiner's statements that "the advantage of these reactive groups is that they are photoactivatable" (citing paragraph [0154]), and "the advantage of photoactivatable reactive groups is that the resulting phosphate-binding compound that is useful for conjugation to phosphorylated target molecules" (citing paragraph [0153]) are completely irrelevant to the patentability of claim 25. The Examiner's conclusion that "it would have been obvious to modify Zimmerman with the reactive groups of Agnew in order to gain the advantages of having a resulting phosphate-binding compound that is useful for conjugation to phosphorylated target molecules" is likewise irrelevant. The pending claims do not encompass reactive groups at all, nor is there any teaching or claim to photoactivatable reactive groups. The undersigned attorney respectfully suggests that the Examiner review the Specification, claims and cited reference once again in order to more fully understand the claimed invention and the art.

Applicants respectfully submit that the rejection of claim 25 under 35 U.S.C. § 103(a) over Zimmerman in view of Agnew has been overcome, and request withdrawal of the rejection.

Claims 26–27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman, *supra*, in view of Strosberg *et al.* (EP 1 178 318 A1, hereinafter "Strosberg"). The Examiner alleged that Strosberg teaches using a multi-protein complex that comprises a recombinant bait protein comprising a fusion tag (citing column 37 line 38–column 39 line 60). The Examiner stated that Strosberg teaches that these recombinant bait proteins can be used as marker compounds, which have the art- recognized benefit of providing a visible method of determining whether two compounds have interacted, and that Strosberg also teaches that the

benefit of these recombinant bait proteins is that they bind specifically to the polypeptide of interest. The Examiner alleged that it would have been obvious for one of ordinary skill in the art to use a recombinant bait protein with a fusion tag in order to bind to a specific polypeptide of interest and to gain the additional advantages and predictable result of optically determining when that polypeptide has been bound to the recombinant bait protein.

Applicants respectfully traverse this rejection. As pointed out above, the claims require the use of an extraction channel. ***Neither Zimmerman nor Strosberg teach the use of an extraction channel***, and hence the combined references cannot teach the limitations of the pending claims. Without addressing the specific points raised by the Examiner, Applicants reiterate that the alleged teaching by Strosberg of the use of recombinant bait proteins as marker compounds does not remedy the deficiencies of the cited references in failing to teach each element of claims 26 and 27, specifically the use of an extraction channel.

Accordingly, Applicants respectfully submit that the rejection of claims 26–27 under 35 U.S.C. § 103(a) over Zimmerman in view of Strosberg has been overcome, and request withdrawal of the rejection.

VIII. EXAMINER'S RESPONSE TO ARGUMENTS

The Examiner stated that Applicant's arguments with respect to claims 1–40 have been considered but are moot in view of the new ground(s) of rejection. Applicants note however that rejections over Laursen and Hagen were withdrawn, and new grounds based on those references were not forthcoming. Thus, Applicants acknowledge the implicit patentability of the instant claims over these references.

CONCLUSION

Entry of this Amendment is respectfully requested. An early and favorable action on the merits is earnestly solicited.

The Commissioner is hereby authorized to charge $555 for a three-month extension of time to Deposit Account No. 50-2852. In the event that an extension of time is required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely. The Commissioner is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-2852.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 565-8185.

Date: December 19, 2008

Respectfully submitted,

/Cynthia R. Moore/
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Reg. No. 46,086

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